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The impact of radiotherapy on patient-reported outcomes of immediate implant-based breast reconstruction with and without mesh

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Mini-abstract

Postmastectomy radiotherapy (PMRT) improves breast cancer outcomes but increases complications following implant-based breast reconstruction (IBBR). This prospective cohort study explored the impact of PMRT on patient-reported outcomes 18-months following IBBR showing worse scores in the PMRT group. These results should be discussed with patients to support informed decision-making for treatment.

ABSTRACT

Objective: To explore the impact of postmastectomy radiotherapy (PMRT) on patient-reported outcomes (PROs) of implant-based breast reconstruction (IBBR) performed with and without mesh.

Summary background data: Post-mastectomy radiotherapy (PMRT) is increasingly given to improve breast cancer outcomes but can adversely impact complications following IBBR. Little, however, is known about the impact of PMRT on the PROs of IBBR, especially when mesh is used.

Methods: The iBRA (implant Breast Reconstruction evAluation) prospective cohort study recruited consecutive women undergoing immediate IBBR from 81 UK breast and plastic surgical units. Demographic, operative, oncological and 3-month complication data were collected, and patients consented to receive validated PRO questionnaires at 18-months. The association between IBBR, PMRT and PROs were investigated using mixed-effects regression models adjusted for clinically-relevant confounders and including a random-effect to account for potential clustering by center

Results: 1163 women consented to receive 18-month questionnaires of whom 730 (63%) completed it. Patients undergoing PMRT (214 patients) reported worse PROs in three BREAST-Q domains: satisfaction with breasts (-6.27 points, $p=0.008$, 95% confidence interval (CI)[-10.91,-1.63]), satisfaction with outcome (-7.53 points, $p=0.002$, CI[-12.20,-2.85]) and physical well-being (-6.55 points, $p<0.001$, CI[-9.43,-3.67]). Overall satisfaction was worse in the PMRT group (OR 0.497, $p=0.002$, CI [0.32, 0.77]). These effects were not ameliorated by mesh use.

Conclusions: PMRT may adversely affect PROs following IBBR irrespective of whether mesh is used. These findings should be discussed with all patients considering IBBR and when

indications for PMRT are borderline to enable informed decision-making regarding oncological and reconstructive treatment options.

Trial registration: ISRCTN37664281

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, with a global incidence of 2.09 million cases in 2018¹. Treatment with curative intent involves surgery, often in combination with systemic treatment and radiotherapy². Despite improvements in cancer treatment, approximately 40% of all women will receive mastectomy as the surgical management of their disease³. Mastectomy may profoundly impact women's well-being and immediate breast reconstruction can improve health-related quality of life (HRQL)^{4,5}.

Implant-based breast reconstruction (IBBR) is the most commonly performed reconstructive procedure in both the UK and US^{6,7}. It can achieve good cosmetic results and offers patients a shorter operation and more rapid recovery than autologous alternatives without donor-site morbidity⁸. Traditionally, IBBR has been a two-stage procedure, involving placement of a subpectoral tissue-expander, sequential expansions with saline to reach the final volume and subsequent replacement of the expander with a permanent implant. However, the introduction of a range of biological (e.g. acellular dermal matrix [ADM]) and synthetic (e.g. titanium-coated polypropylene) meshes has led to the development of single-stage direct-to-implant IBBR techniques. Mesh-assisted sub-pectoral reconstruction involves suturing a mesh between the lower edge of the pectoralis muscle and the chest wall, creating an extended pocket that can accommodate a fixed-volume implant in one procedure⁹. More recently, pre-pectoral techniques have been introduced. These spare the muscle entirely by wrapping the implant in mesh and placing it on top of the pectoralis muscle¹⁰. Whilst new IBBR techniques have become widely adopted into practice, there is a paucity of high-quality evidence to support their safety and effectiveness, particularly in the context of postmastectomy radiotherapy (PMRT)¹¹.

Post-mastectomy radiotherapy (PMRT) improves breast cancer survival and reduces local recurrence¹²⁻¹⁵, but treatment was traditionally restricted to patients with locally-advanced disease (large tumours and/or significant nodal disease). More recently, evidence has emerged to suggest that PMRT may reduce recurrence and improve long-term survival in intermediate risk patients, in particular those with one to three positive nodes¹⁶. Increasing numbers of women are therefore recommended treatment.

The offer of IBBR in the context of anticipated PMRT remains controversial^{17,18}. Radiotherapy may result in skin changes, fibrosis and impaired vascularity and has been shown to be an independent risk-factor for complications following IBBR¹⁹. In the longer term, capsular contracture following PMRT is a significant problem leading to pain and deformity that often requires surgery to remove the implant or replace it with autologous tissue²⁰. Using biological mesh to provide implant coverage, however, has been shown to reduce levels of myofibroblasts, fibroblasts, and other markers of inflammation and fibrosis following PMRT²¹ and there is limited evidence to suggest reduced rates of capsular contracture when biological mesh is used²². This may improve outcomes for patients undergoing surgery but there is little published literature on the impact of PMRT on patient-reported outcomes (PROs) on IBBR, especially in the context of newer mesh-assisted techniques.

A 2017 systematic review found six studies (593 patients) that evaluated patient satisfaction after IBBR and PMRT²³. The majority of included studies used non-validated questionnaires and the proportion of satisfied patients varied widely²⁴⁻²⁹. Four studies (575 patients) used the validated BREAST-Q questionnaire and demonstrated that patients receiving PMRT reported globally worse scores in all domains. None of these studies, however, reported the use of newer single-stage mesh-assisted techniques²³. More recently, a prospective multicenter

cohort study which included 1604 patients receiving both two-stage and single-stage IBBR reported reduced satisfaction with breasts associated with radiotherapy (224 irradiated patients, 811 non-irradiated) at 1 and 2 years post-operatively¹⁹ but did not report details of the direct-to-implant techniques used. Smaller retrospective cross-sectional studies have produced conflicting evidence regarding the impact of PMRT on PROs following IBBR³⁰⁻³². With the use of both PMRT and IBBR increasing and recent recommendations that reconstruction should be offered to all women, even if PMRT is anticipated², there is an urgent need for high-quality research to explore the impact of radiotherapy on the outcomes of implant-based procedures to help patients make informed decisions about their reconstructive and oncological options³³.

The iBRA (implant Breast Reconstruction evAluation) study is a four-phase study aiming to inform the feasibility, design, and conduct of a future trial in immediate IBBR¹¹. Phase 2, a UK prospective multicenter cohort study, explored the clinical and patient-reported outcomes of different approaches to immediate IBBR with and without mesh. The short-term safety outcomes have been reported elsewhere⁹. Here we report the 18-month PROs of IBBR in patients undergoing surgery for malignancy to explore the impact of PMRT on patient satisfaction and HRQL and determine whether this is influenced by the use of biological mesh.

METHODS

iBRA study design and procedures

The iBRA study prospectively recruited consecutive women aged 16 years or older undergoing immediate IBBR for malignancy or risk-reduction between Feb 1, 2014 and June 30, 2016. All UK breast or plastic surgical units performing immediate IBBR were invited to participate via

the UK Trainee Collaborative Research Network, the Association of Breast Surgery and the British Association of Plastic Reconstructive and Aesthetic Surgeons¹¹.

Patients at participating centers undergoing IBBR using any technique were eligible for inclusion. This included subpectoral reconstructions with and without mesh, and pre-pectoral techniques. Patients were excluded if undergoing delayed reconstruction or receiving an implant in combination with an autologous flap¹¹. Patients undergoing neoadjuvant chemotherapy or endocrine therapy prior to IBBR were eligible for inclusion.

Eligible patients were prospectively identified from clinics, multidisciplinary team (MDT) meetings, and theatre lists. Demographic, operative, oncological and 3-month complication data were collected by the team by clinical or case-note review. Patients who consented to participate in the PROs study were sent electronic or postal questionnaires, according to their preference, at 3- and 18-months after surgery. The 3-month questionnaire focused on satisfaction with information, adjuvant treatment and complications while the 18-month questionnaire included BREAST-Q domains relating to satisfaction with outcome and quality of life. Reminders were sent after 1 month if no response had been received. Data on PMRT were collected by clinical report of treatment recommendations by the MDT and patient self-report at 3 or 18-months. Follow-up was complete in December 2017. Anonymized data were recorded using REDCap, a secure online database^{11,34}.

All patients had skin or nipple-sparing mastectomy with immediate IBBR. Procedural details were recorded but no restrictions were placed on the techniques (e.g. one or two stage; type of implant or expander; types of mesh) used, as this study aimed to explore current practice and inform a future trial¹¹. Reconstructive techniques were categorized for analysis as: standard two-stage submuscular/subfascial, subpectoral with biological mesh, synthetic

mesh, or dermal sling, pre-pectoral, and other. Product choice, implant positioning and use of laminar flow, antibiotics and drains were according to local policy or surgeon preference. Adjuvant therapies were as recommended by the multidisciplinary team.

Study governance and consent to participate

Ethics approval was not required, as the study was defined as service evaluation by the Health Research Authority (HRA) decision tool (<http://www.hra-decisiontools.org.uk/research/>). Local audit approval was obtained for each center before commencing study recruitment. Clinical and PRO data were collected as recommended by guidelines for best practice³⁵.

Patients were approached for written consent to receive questionnaires by members of the clinical team either in clinic or during their hospital stay, according to local study team preference. This was consistent with the methodology used in the UK National Mastectomy and Breast Reconstruction Audit (NMBRA)³⁶. Where consent was obtained, patient contact details were sent securely to the coordinating center and questionnaires distributed centrally to optimize compliance, allow accurate follow-up and minimize missing data¹¹.

Patient population

Women from the iBRA cohort who underwent at least one procedure for malignancy (invasive breast cancer or ductal carcinoma in situ) and returned the 18-month questionnaire were eligible for inclusion in this analysis. Excluded were patients who underwent exclusively risk-reducing surgery and those for whom PMRT or PRO data were unavailable.

Outcomes

This study reports the 18-month PROs of IBBR with and without PMRT in patients undergoing surgery for malignancy in the iBRA study.

PROs were assessed using the validated BREAST-Q Post-Operative Reconstructive module (version 1). The BREAST-Q is a validated questionnaire robustly developed using Rasch methodology for use in a breast reconstruction population and includes six domains: satisfaction with breasts; satisfaction with outcome; physical, psychosocial and sexual well-being^{37,38}. This was selected as it assessed key PRO domains included in the reconstructive breast surgery core outcomes set³⁹. The 18-month questionnaire also included a single-item assessment of overall satisfaction outcome on a five-point Likert scale; excellent, very good, good, fair and poor, as per the NMBRA³⁶.

Statistical analysis

Patients were categorized as having received PMRT (RT group) or not (non-RT group). Patients who reported in either the 3-month and/or 18-month questionnaire as having received PMRT were included in the RT group. If no patient-reported information was available on radiotherapy, patients were classified based on adjuvant therapies recommended at MDT.

Simple summary statistics were used to describe patient demographics, procedures performed to the breast and axilla; postoperative oncological data and MDT decision-making, 3-month complications and 18-month PROs across the patient groups (responders vs. non-responders and +/-PMRT). Categorical data were summarized by counts and percentages, and continuous data by median, upper and lower quartiles, and range. The characteristics of patients receiving/not receiving PMRT who completed the questionnaire were compared using t-tests and chi-squared tests for continuous and categorical variables respectively.

Questionnaire responses for the BREAST-Q domains were summed and transformed according to the developers' instructions using the specifically designed Q-Score software⁴⁰. This generated a score from 0 to 100 for each domain where higher scores indicate greater patient satisfaction or HRQL³⁷. BREAST-Q scores were treated as continuous variables. For the purpose of analysis, the single-item overall outcome score was dichotomized into 'excellent/very good' and 'good/fair/poor'.

The effect of radiotherapy on each outcome domain was explored using multivariable mixed-effects linear and logistic regression models, including a random effect to account for potential clustering by center. Models were adjusted for clinically-relevant confounders identified by the study steering group based on the literature and clinical expertise. These confounders were: age, body mass index (BMI), smoking status, ASA (American Society of Anesthesiologists) grade, bilateral surgery, nipple-sparing versus other mastectomy types, reconstructive technique (standard two-stage submuscular/subfascial, subpectoral with biological mesh, synthetic mesh, or dermal sling, pre-pectoral, and other), 3-month complications (infection, implant loss, readmission or reoperation), axillary surgery and adjuvant chemotherapy and endocrine therapy. A complete case analysis was undertaken, and robust residual estimates were used to ensure the assumptions of the regression models were not violated. The action of biological mesh as an effect modifier in the regression models was checked using an interaction term.

This study was registered (ISRCTN37664281) and is reported according to STROBE guidelines⁴¹. The protocol was published in 2016¹¹ and short-term outcomes published in 2019⁹.

RESULTS

The iBRA study recruited 2108 patients from 81 centers between February 1, 2014, and June 30, 2016, of whom 1693 (80%) underwent surgery for malignancy. The remaining 415 (20%) who underwent exclusively risk-reducing surgery were excluded from the analysis. A further 56 (3%) patients were excluded as they had no information regarding PMRT. 1164 (71%) of the remaining 1637 eligible patients consented to participate in the PROs study and 730 (63%) returned the 18-month questionnaire (figure 1).

Patients consenting to receive PRO questionnaires were demographically representative of the cohort of patients with malignancy (Appendix 1). However, patients returning the questionnaires were older (median 51.5, interquartile range [IQR] 46-60 vs. 49, IQR 43-57) and were less likely to smoke (n=58, 8% vs n=65, 15%) or have experienced major complications in particular implant loss at 3-months (n=39, 5% vs n=62, 14%) than non-responders. Full cohort demographic details by PRO status and PMRT group are summarized in Appendix 2.

Participant demographics

Of the 730 patients completing the 18-month questionnaire, 214 (29%) patients were included in the PMRT group; 203 patients who self-reported receipt of radiotherapy at either 3 or 18-months and 11 patients who did not complete the adjuvant treatment sections of the questionnaires but were recommended radiotherapy by the MDT and therefore considered to have received it. 516 patients (71%) were not recommended radiotherapy and did not report having received treatment so were included in the non-RT group.

Patients who received PMRT were younger than those who did not, but there was no evidence of a difference in BMI or smoking status between the groups (table 1). Patients receiving PMRT were more likely to undergo an axillary node clearance (ANC) at the time of reconstruction

than patients not undergoing PMRT, but there were no differences regarding the planned type of reconstruction (single vs two-stage); technique (use or type of mesh); type of prosthesis (tissue expander vs fixed volume implant) or percentage of patients undergoing bilateral surgery. Three-month complication rates were similar between the groups (table 2). Patients who underwent PMRT were more likely to have received neoadjuvant chemotherapy, have grade 3 cancers, larger tumours and involved lymph nodes (table 3).

Outcomes

Table 3 summarizes the 18-month PROs for patients undergoing IBBR by receipt of PMRT. The number of responses that were sufficiently complete to be used for analysis were similar for each domain, and percentage responses were similar between the radiotherapy groups, excepting sexual well-being which was an optional scale and had fewer complete responses in the PMRT group (table 4). Median BREAST-Q scores were lower in the PMRT group across all domains. Similar results were observed for the single-item assessment of overall outcome, with fewer patients in the PMRT group considering their reconstruction to be 'excellent' or 'very good' (table 4).

Mixed-effects linear regression models were used to evaluate the impact of radiotherapy on BREAST-Q scores (table 5). In this analysis, there was evidence that patients receiving PMRT reported lower scores in three of the five BREAST-Q domains: satisfaction with breasts, satisfaction with outcome and physical well-being, but there was no evidence of a difference between groups in scores for sexual or psychosocial well-being. Patients who received radiotherapy were less likely to report an 'excellent' or 'very good' overall outcome than those who did not (OR 0.497, $p=0.002$, CI[0.32, 0.77]).

Interaction terms examined the action of biological mesh as an effect modifier in the regression models. There was no evidence that biological mesh modified the association between radiotherapy and satisfaction with breasts (interaction coefficient=3.39, $p=0.191$, CI[-1.70-8.48]), satisfaction with outcome (interaction coefficient=4.78, $p=0.173$, CI[-2.09-11.65]), psychosocial well-being (interaction coefficient=4.97, $p=0.133$, CI[-1.52-11.46]), physical well-being (interaction coefficient=-0.09, $p=0.973$, CI[-5.01-4.84]) or overall outcome (OR for interaction=1.09, $p=0.826$, CI[0.52-2.26]). Biological mesh was associated with a reduced impact of radiotherapy on sexual well-being (coefficient=13.37, $p=0.001$, CI[5.61-21.13]).

DISCUSSION

This multicenter prospective cohort study of 730 patients undergoing IBBR with and without mesh demonstrates that women receiving PMRT reported worse PROs at 18-months following surgery in key HRQL domains: satisfaction with breasts, satisfaction with outcome and physical well-being. They were less likely to describe the outcome of their reconstruction as 'excellent' or 'very good' compared with patients who did not receive PMRT. These effects were not ameliorated by the use of biological mesh and exceed the recently-reported minimum clinically-important difference of 4 points for the BREAST-Q⁴². Furthermore, the scores reported here are similar to those reported by patients undergoing mastectomy only in the UK NMBRA³⁶. These findings should be discussed with patients considering IBBR in whom PMRT may be indicated or when PMRT recommendations are borderline to help them make informed decisions about their reconstructive and oncological treatment options, bearing in mind that some women may risk a decrease in satisfaction

with their reconstruction, rather than undergoing simple mastectomy, which may be the only alternative.

Several studies^{19 23,30-32,43-46} have evaluated the impact of PMRT on the patient-reported outcomes of IBBR but many of these are small, retrospective and have significant methodological limitations including the use of non-validated PROMs²⁴⁻²⁹ which cannot reliably be compared between studies²³. Furthermore, much of the evidence to date focuses predominantly on traditional two-stage expander-implant IBBR²⁴⁻²⁶. Evidence regarding the impact of PMRT on newer mesh-assisted-techniques is lacking²³. This study provides much needed data to support modern reconstructive practice and suggests that consistent with the findings of previous work, PMRT adversely affects the PROs of IBBR, even if mesh is used.

Although several studies suggest that acellular dermal matrix may reduce capsular contracture following PMRT^{21,47}, the current data do not suggest that this translates into improved PROs when biological mesh is used. Reasons for this are likely complex and may indicate that satisfaction is a multidimensional construct that reflects more than objective measures such as capsular contracture. Additionally, patients in the current study underwent predominantly mesh-assisted subpectoral reconstruction. Further work is now needed to determine if similar results are seen following prepectoral reconstruction as emerging data suggests the effects of PMRT may be less marked when the implant is placed on top of, rather than under the muscle^{47,48}.

This is, to our knowledge, the largest prospective study to explore the impact of PMRT on single-stage IBBR with and without mesh but has limitations. Firstly, it represents an exploratory post-hoc analysis of a subset of patients with malignancy in the iBRA study that

was not initially planned and there is the possibility of significant results by chance due to multiple testing. The concordance between the current findings and existing published data¹⁹, however, suggests this is unlikely.

In addition, this is an observational study and therefore at risk of potential biases such as confounding. Although there were no obvious demographic differences between patients who consented to receive post-operative questionnaires and those who did not, there were clear differences between the patients who completed the questionnaires and non-responders. Non-responders were more likely to be younger and have experienced major complications at 3-months than those who participated, raising the possibility of response bias which may have impacted the results. Patients who received PMRT were more likely to have more locally-advanced disease than those who were not recommended treatment. Attempts were made to adjust for known confounders such as additional oncological treatments, but the study may still be subject to bias due to subtler differences between the patient groups. As a randomized clinical trial in this context would not be feasible, observational data will provide the best possible evidence of the impact on PMRT on the PROs of IBBR.

The study was pragmatically designed to optimize participation and recruitment, but this limited our ability to optimize data quality and completeness. As a complete case analysis was performed, the number of patients included in the regression models was limited by missing data. There is potential for bias to be introduced due to the missingness and interaction term tests for effect modifiers are likely to be underpowered in this analysis. Future studies should identify key variables for inclusion and use methods to maximize data completion. Finally, this study assessed PROs 18 months post-operatively. While these data

are important, the effects of PMRT are likely to evolve over time and longer-term outcomes would ideally be needed to fully evaluate the impact of PMRT.

There is growing evidence to suggest that PMRT adversely impacts the early (up to 18-month) PROs of IBBR. These data should be discussed with patients to help them make informed decisions about reconstructive surgery. Further work is now needed to explore whether similar effects are seen with newer prepectoral techniques and to establish if and how PROs change over time. Work is also needed to determine the absolute benefit of PMRT. Current decision making is based on historic data¹⁶ and the results of studies such as SUPREMO⁴⁹ are awaited to determine whether PMRT does improve oncological outcomes in intermediate risk groups in an era of modern systemic treatment. Other novel methods for predicting radiotherapy benefit may also have utility in this group⁵⁰. Such developments will improve decision-making in the future but currently clear communication of the potential risks and benefits of both IBBR and PMRT are needed to ensure that patients, in partnership with the multidisciplinary healthcare team, make fully-informed decisions regarding their breast cancer treatment and reconstructive options.

AUTHORS' CONTRIBUTIONS

SP, CH, ST, JS, NB, RIC and LW conceived the study; SP, NT and ES planned the analysis; NT and EJC supported ES in undertaking the analysis; all authors contributed to data interpretation. ES and SP wrote the first draft of the manuscript. SP is the guarantor. All authors reviewed and critically revised the manuscript and approved it prior to submission.

AUTHOR ACCESS TO DATA

The authors had full access to the data contained in this manuscript.

CONFLICTS OF INTEREST, INCLUDING FINANCIAL INTERESTS, ACTIVITIES, RELATIONSHIPS, AND AFFILIATIONS

The authors have no conflicts of interest to declare.

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Figure 1: Patients included in the 18 month patient reported outcome study